CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-739

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 74-739 DRUG PRODUCT: Amiodarone Tablets

FIRM: Copley Pharmaceutical Co. DOSAGE FORM: Tablets

STRENGTHS: 200 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 11/9/98

BIO INFORMATION: Satisfactory by Moo Park 9/25/96.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The product is a non-compendial drug product. Methods validation (Phila-DO) is satisfactory as of 8/11/98. See memo from C. Becoat. (The firm revised their original method and methods validation was repeated).

The firm tests the finished dosage form by incorporating the following tests:

Finished Product Specifications for Amiodarone Tablets, 200

Test	Specification
Appearance	Meets Description
Identification	
Dissolution Apparatus II	s
Related Substances	Individual at Release Individual on Stability NMT Total at Release Total on Stability
Uniformity of Dosage Units <905>	Meets Requirements
Assay	label
Moisture	

STABILITY-
Page 2753

Protocol Stability determined in smallest and largest containers; pilot lot placed on accelerated stability (40°C/75% RH/1,2,3 months); first three production lots placed on long term studies (25°C - 30°C/ 0,3,6,9,12,18,24 months); sampling is representative of batch, units for testing are removed randomly; samples tested for appearance, assay , dissolution , related substances (NMT individual, NMT total).
Stability Commitment page 2767 - first three production lots and one production lot thereafter to be placed on RT (25°C - 30°C/ 0,3,6,9, 12,18,24 months) study; results reported in AR; lots that fail specs will be withdrawn.

Expiration Date 24 months based on accelerated stability data.

Stability Data page 2771; see attachment 7; only accelerated stability data is included. Data is satisfactory. Note - 100's at 1 month station passed dissolution at S2 level only.

LABELING-Satisfactory. See review dated 11/9/98.

STERILIZATION VALIDATION - Not Applicable

SIZE OF BIO BATCHES-

Process Summary:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-739** Date of Submission: **April 7, 1998**

Applicant's Name: **Copley Pharmaceutical Inc.**

Established Name: **Amiodarone Hydrochloride Tablet**

Labeling Deficiencies:

1. CONTAINER 200 mg - 60s, 100s, and 250s

   Satisfactory in final print.

2. INSERT

   Due to changes in the labeling of the reference listed drug (Cordarone®; Approved June 15, 1998; Revised February 20, 1998), we request you revise your insert labeling as follows:

   a. WARNINGS

      Insert the following text to appear as the subsection following "Liver Injury":

      Loss of Vision

      Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of amiodarone therapy. The risks and complications of antiarrhythmic therapy with amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias.

Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of amiodarone. (See ADVERSE REACTIONS.)

b. PRECAUTIONS

i. Corneal Microdeposits; Impairment of Vision - Revise this subsection to read as follows:

Impairment of Vision

Optic Neuropathy and/or Neuritis
Cases of optic neuropathy and optic neuritis have been reported (see WARNINGS).

Corneal Microdeposits
Corneal microdeposits appear in the majority of adults treated with amiodarone. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose ~~of~~ or termination of treatment. Asymptomatic microdeposits alone are not a reason to reduce dose or discontinue treatment (see ADVERSE REACTIONS).

ii. Insert the following subsection following "Impairment of Vision":

Neurologic

Chronic administration of oral amiodarone in rare instances may lead to the development of peripheral neuropathy that my resolve when amiodarone is discontinued, but this resolution has been slow and incomplete.

c. ADVERSE REACTIONS

i. Insert the following text to appear as the fourth paragraph:

Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma,

lens opacities, and macular degeneration have been reported. (see WARNINGS)

ii. Insert the following text to appear as the eighth paragraph:

Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, angioedema, bronchiolitis, obliterans organizing pneumonia (possibly fatal), pleuritis, pancreatitis, toxic epidermal necrolysis, pancytopenia, and neutropenia also have been reported in patients receiving amiodorone.

iii. Delete the second paragraph under "The following side effects were each reported in less than 1% of patients".

Please revise your insert labeling, as instructed above and submit final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

COPLEY PHARMACEUTICAL, INC.

MINOR AMENDMENT
Amidarone Hydrochloride Tablets 200 mg
ANDA # 74-739

Field Copy Certification

This is to certify that the field copy submitted in accordance with 21 CFR § 314.94 (d)(5) is a true copy of the technical section of our amendment for Amiodarone Hydrochloride Tablets 200 mg.

Amidora Nud

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

10/13/98
Date

NV

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-739 Date of Submission: December 3, 1996

Applicant's Name: Copley Pharmaceutical Inc.

Established Name: Amiodarone HCl tablet

Labeling Deficiencies:

1. CONTAINER 200 mg - 60s, 100s, and 250s

   Upon further review, please revise the storage temperature recommendations to read as in your original submission:

   Store at room temperature, approximately 25°C (77°F).

2. INSERT

   a. DOSAGE AND ADMINISTRATION

      Relocate "Adjustment and Maintenance Dose" so that it appears centered above the last two columns of the table.

   b. HOW SUPPLIED

      i. See comment under CONTAINER above.

      ii. Include "200 mg" with the established name.

Please revise your labels and labeling, as instructed above and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
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